Chronic heroin use disorder and the brain: current evidence and future implications

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ABSTRACT

The incidence of chronic heroin use disorder, including overdose deaths, has reached epidemic proportions. Here we summarise and evaluate our knowledge of the relationship between chronic heroin use disorder and the brain through a narrative review. A broad range of areas was considered including causal mechanisms, cognitive and neurological consequences of chronic heroin use and novel neuroscience-based clinical interventions. Chronic heroin use is associated with limited or very limited evidence of impairments in memory, cognitive impulsivity, non-planning impulsivity, compulsivity and decision-making. Additionally, there is some evidence for certain neurological disorders being caused by chronic heroin use, including toxic leukoencephalopathy and neurodegeneration. However, there is insufficient evidence on whether these impairments and disorders recover after abstinence. Whilst there is a high prevalence of comorbid psychiatric disorders, there is no clear evidence that chronic heroin use per se causes depression, bipolar disorder, PTSD and/or psychosis. Despite the growing burden on society from heroin use, knowledge of the long-term effects of chronic heroin use disorder on the brain remains limited. Nevertheless, there is evidence for progress in neuroscience-based interventions being made in two areas: assessment (cognitive assessment and neuroimaging) and interventions (cognitive training/remediation and neuromodulation). Longitudinal studies are needed to unravel addiction and neurotoxic mechanisms and clarify the role of pre-existing psychiatric symptoms and cognitive impairments.

Keywords: fMRI, heroin, neurocognition, neuroimaging, neuroscience, sMRI, neurology, interventions.

1. Introduction

This review aims to summarise current knowledge of chronic heroin use disorder with regard to the brain and highlight areas of progress. A characteristic feature of chronic heroin use disorder includes a strong desire to use opioids, manifested by an impaired ability to control use despite harm and negative consequences (American Psychiatric Association, 2013).

By conceptualizing heroin use disorder as a chronic brain disorder, clinicians can better understand the course and treatment of its many complications, how to achieve and sustain remission in dependency and help prevent relapse.

2. Epidemiology

The increasing incidence of opioid use disorder, including overdose deaths, has reached epidemic proportions (Kreek et al., 2019). About 275 million people worldwide, 5.6 per cent of the global population aged 15–64 years), used drugs at least once during 2016 (World Drug Report, 2019). Amongst these were about 34 million people who used opioids and about 19 million who used opiates. Roughly 450,000 people died as a result of drug use in 2015 and those deaths (Larochelle et al., n.d.). The lifetime prevalence of witnessed overdoses among drug users is about 70%. The US has the highest prevalence of opioid use, near to 4 per cent of the population aged 15–64 (World Drug Report, 2019). About 2.1 million Americans have opioid use disorder and opioids were involved in more than 47,600 deaths in 2017 in the US accounting for more deaths than road traffic accidents and gun

violence combined (Rudd et al., 2016). Over 4.3 million Americans are engaged in non-medical use of prescription opioids per month and 4.8 million people have used heroin at some point in their lives. From each year since 2002, estimates of past month heroin use, past year heroin use, and opioid (heroin) use disorder have increased amongst 18-25 year old ("Data Overview | Drug Overdose | CDC Injury Center," n.d.).

Approximately two-thirds of current people who primarily use heroin additionally use prescription opioids and there is evidence that the first opioid abused is most frequently a prescription opioid rather than heroin, as was the case in the 1960s through 1980s (Philips and Ford, 2017). Illicit use of fentanyl, a highly potent synthetic opioid often used to "cut" heroin, has increased in the United States, contributing to a very substantial rise in fatal overdoses (Larochelle et al., 2018).

There have been steps taken at a global level to set strategies for a response to this grave situation, particularly over the past decade. The Joint UN Ministerial Political Declaration and Plan of Action in 2014 (Commission on Narcotic Drugs opens its 57th session in Vienna) explicitly reaffirmed that SUD is a health problem with a need to further strengthen public health systems that are responsive to current and emerging drug-related problems. The adoption of the Sustainable Development Goals also reaffirms this vision of strengthening the prevention and treatment of substance abuse, including narcotic drug abuse and harmful use of alcohol. The outcome document of the special session of the United Nations General Assembly on the World Drug Problem held in 2016 (UNGASS, 2016) contains more than 100

recommendations for promoting evidence-based prevention, care and other measures to address both supply and demand. Additionally, WHO and UNODC have developed a close collaboration to support the implementation and development of comprehensive, integrated health-based approaches to drug policies, that can reduce demand for illicit substances, relieve suffering and decrease drug-related harm to individuals, families, communities and societies (International Standards for the Treatment of Drug Use Disorders Draft for Field Testing).

3. Clinical presentation of chronic heroin use

3.1. Neuroadaptation ad impairment

The term chronicity describes the repeated administration of opioid drugs with the adaptive mechanisms changing the functioning of opioid-sensitive neurons and neural networks perhaps in an irreversible or hard-to-reverse manner(Christie, 2008). Neuro-adaptation is particularly a consequence of sustained mu receptor stimulation by opioid drugs (Kieffer and Evans, 2002). Hallmarks of neuroadaptations to chronic opioid use are:

- Tolerance, defined as reduced sensitivity to acute opioid effects (e.g. euphoriant and analgesic effects);
- Physiological manifestations of opioid withdrawal on abstinence;

- Drug craving and attention directed towards drug-seeking and drug intoxication.

Neuroadaptations following chronic heroin exposure extend well beyond reward circuits to other brain systems, notably those involved in cognition and stress responses (Koob and Volkow, 2016). Important brain regions affected include the amygdala, hippocampus and cerebral cortex and their connections to the nucleus accumbens. Cognitive maladaptation is an umbrella term for any "neuroadaptation" resulting from extreme saliency (importance or value) of drug reward. High sensitivity to short term reward and preferred attention to drug-related cues are some examples of cognitive maladaptation in substance users that could be potentially be addressed using cognitive 2

3.2. Neurocognitive impairments

As above, opioids have been associated with a number of neuropsychological impairments during both chronic use and after a period of abstinence (Verdejo-García and Pérez-García, 2007). Neuropsychological studies of chronic opioid users have identified deficits in executive functions. including impairments in cognitive flexibility (Pirastu et al., 2006), strategic planning (Ersche et al., 2006; Ersche and Sahakian, 2007), decision making (Verdejo-García et al., 2007; Verdejo-García et al., 2007) and inhibitory control (Mintzer et al., 2005). However other studies found no clear deficits when comparing the performance of healthy controls, with that of opioid abstinent, polysubstance users, head injury patients or patients with chronic pain (Jamison et al., 2003).

The accumulated literature tends to assume that neuropsychological function is to some extent impaired as a consequence of chronic opioid use and that the impairments are different from that seen in acute and sub-acute users (Zacny, 1995). Meta-analytical research has shown that chronic heroin use is associated with moderate deficits in verbal fluency, verbal working memory, inhibitory control, planning and risk and reward-based decision-making (Baldacchino et al., 2012). More recent studies have revealed visual memory, working memory impairments, impulsivity and compulsivity among chronic heroin users, including those enrolled in MMT and abstinent formerly dependent patients (Baldacchino et al., 2015; Tolomeo et al., 2019, 2018, 2016). MMT has generally been associated with additional cognitive impairments, although the specific cognitive domains which are affected remain unclear and may be explained by generalised cognitive slowing, affecting speed of information processing across different tasks, not as specific cognitive deficits (Baldacchino et al., 2012). Interestingly, buprenorphine seems to be a much "cleaner" drug with regard to neuropsychological test results, with most studies showing decision-making improvement relative to MMT associated with buprenorphine treatment (Baldacchino, Steele, Davey, Tolomeo, 2019).

Although research in this area is limited, it seems to point to a general improvement in at least some areas of neuropsychological functioning after at least 2 weeks of abstinence from heroin use. This suggests that some of the impairments observed in active heroin users are transient effects of intoxication by the drug itself. In one observational study by Baldacchino et al. (Baldacchino et al., 2015) and three studies by Tolomeo et al. (Tolomeo et al., 2019, 2018, 2016), abstinent, previously heroin-dependent individuals showed significantly higher cognitive and

non-planning impulsivity, and impaired flexibility and visuospatial memory when compared with healthy controls. Longitudinal studies are however required to clarify this issue.

3.3. Psychiatric Illness

Many studies have found a significant prevalence of depression, anxiety and/or Post-Traumatic Stress Disorder (PTSD) in individuals with heroin use disorders which is also associated with worse treatment outcome and prognosis. These findings suggest the importance of identifying and treating psychiatric disorders among heroin-dependent individuals, since the effective treatment of psychiatric co-morbidity potentially improves prognosis for heroin use disorder (Hasin et al., 2004; Hassan et al., 2017). However, there is no clear evidence to support the hypothesis that heroin use, per se, increases the risk of these psychiatric disorders through possible molecular and/or cellular pathways. Similarly, a direct relationship between opioid use and psychosis including schizophrenia is unclear. Theoretically though, as chronic opioid use is associated with D2 receptor reduction similar to other addictive substances (G J Wang et al., 1997).

Animal models indicate that early-life stress results in long-term changes in stress responses which can alter the sensitivity of the dopamine system and increase susceptibility to self-administration of substances of abuse (Koob and Schulkin, 2018). While it is difficult to systematically delineate the specific neural basis of comorbidity, these studies provide potential pathways to explore in attempting to

understand the well-established relationship between early-life adversity, psychiatric disorders and opioid use disorders in adolescents and adults (Suh and Ressler, 2018).

3.4. Cerebrovascular Disease

Opioids do not elevate blood pressure; indeed, they can cause bradycardia and vasodilation and so may lead to hypotension and tend not to directly increase the risks of developing an ischaemic or haemorrhagic stroke. Indeed, repeat dose opioids may be used therapeutically to treat breathlessness in chronic heart failure (Oxberry et al., 2013). However long-term opioid use may aggravate the risk of cardiovascular disease by elevating low-density lipoproteins and free triglycerides; these biochemical hallmarks are associated with an increased risk of atherosclerosis, cerebrovascular ischemia, and myocardial infarction.

Particularly relevant to heroin users, the use of non-sterile opioids can substantially increase the risk of ischemic events (Radke et al., 2014). Non-sterile syringes/equipment facilitates the entry and dissemination of organisms into the bloodstream when taking heroin which can cause infarcts. Severe damage to peripheral veins is often particularly noticeable in long-term heroin users. Illicit opiates very often contain contaminants and bacteria, septicaemia and endocarditis are increased in opioid use disorder (Kovacs et al., 2015). Infective emboli may occlude cerebral vessels causing necrosis and stroke. septic arteritis and aneurysm causing intracranial haemorrhage have been reported. Compounding these events

is the increased risk of non-fatal overdoses and consequent hypoxic cerebral damage (Hassan et al., 2019; Pearson et al., 1976; Trescot et al., 2008).

3.5. Other Neurological Diseases

Toxic leukoencephalopathy is a progressive degeneration of the myelin in the white matter which has been reported in opioid users although the pathological mechanism remains unclear (Achamallah et al., 2019). Patients may present with inattention, changes in personality, dysarthria, ataxia, dementia, coma and even death. Pronounced, confluent, subcortical white matter changes are characteristic MRI appearances correlate with degeneration of the deep white matter and axonal damage on postmortem examination. However, due to its rarity, there is no systematic case series published as yet. An increase in the number and distribution of hyperphosphorylated tau-positive neurofibrillary pre-tangles has been noted in populations of young, chronic heroin abusers (Kovacs et al., 2015a). Chronic opioid use is also is associated with neurodegeneration, such as reports of occasional ubiquitin-positive neurons (Kovacs et al., 2015). Consistent with these pathological findings, significant brain atrophy has been recognised in heroin abusers. Detailed understanding of the relationship between these neurological abnormalities and the development of cognitive impairments remains unclear. Lesions in the globus pallidus are a long-recognized consequence of heroin use and are thought to be related to hypoxic injury (Pearson et al., 1976). Other reported neurological disease includes aseptic and septic (bacterial, viral and fungal) meningitis and cerebral abscesses (Risdahl et al., 1998), A review proposed that opiates alter host defences

against infectious disease agents, affected by opioid administration, severity of dependence and dose and route of infection (Risdahl et al., 1998).

4. Pharmacology of chronic heroin use

Opioids act by attaching to three types of receptor; mu, delta, and kappa. These are found both pre- and post-synaptically on neurons predominately within the nucleus accumbens, amygdala and cerebral cortex of the brain. They regulate responses to pain, but also exert effects on satiety, thirst and respiratory drive. The euphoric effects of opioids are thought to arise chiefly via activation of mu-opioid receptors and dysphoric effects by activation of kappa opioid receptors, whereas the analgesic effects are thought to arise via activation of mu, kappa and delta receptors. Drugs that stimulate mu-opioid receptors increase the firing of dopaminergic neurons in the ventral tegmental area of the midbrain (Fields and Margolis, 2015). These dopaminergic neurons project widely to other parts of the brain, particularly the basal ganglia including the accumbens and the prefrontal cortex. In medicine, causal mechanisms are generally studied using animals. It is usually not possible to establish causal mechanisms in a study on humans because of ethical limitations. However, neuroimaging studies in humans can be used to test whether measures obtained non-invasively are consistent with causal mechanisms hypothesized from studies on animals.

4.1. Functional Neuroimaging

Whilst there is significant experimental evidence implicating the endogenous opioid system (opioid peptides and opioid receptors) with the processes of reward and reinforcement, the functional neuroimaging evidence in clinical populations is limited. Regarding fMRI, most task-based fMRI studies have explored drug/stress cue-reactivity paradigms (Langleben et al., 2008; Tabatabaei-Jafari et al., 2014; Wang et al., 2011) and only a few have explored response control and decision-making paradigms to investigate hypothesised brain region or network dysfunctions in people with heroin use disorder. For example, Gradin and colleagues reported disrupted reward processing within the striatum and increased sensitivity to aversive events within the amygdala and hippocampus in patients receiving Methadone Maintenance Therapy (MMT) (Gradin et al., 2014). In the same study, the authors reported blunted striatal reward prediction error signals, which can be considered a 'signature' of dopamine system activity (Gradin et al., 2014). A recent systematic review concluded that heroin use is associated with weak fronto-cingulate connectivity with subcortical regions, but strong functional connectivity with the amygdala and striatum (Stewart et al., 2019). Preliminary evidence suggests that functional brain abnormalities within the inferior frontal cortex and anterior cingulate cortex may improve as a function of long-term heroin abstinence (Goldstein and Volkow, 2011).

4.2. Structural Neuroimaging

Grey matter consists of cell bodies, dendrites and synapses that process information in cortical and subcortical brain regions. Brain white matter consists of

myelinated axons that connect grey matter regions. Studies using sMRI have revealed that heroin use is associated with grey matter and white matter reductions, in the striatum, fronto-cortical and cingulate regions, and amygdala and insula (Denier et al., 2013; Liu et al., 2009; Yuan et al., 2009). Additionally, longer opioid use has been reported to be associated with greater grey and white matter reductions in heroin users (Forman et al., 2004; Liu et al., 2009; Yuan et al., 2009). Structural magnetic resonance imaging studies of human opioid-dependent populations have revealed significant grey matter reductions in the prefrontal and temporal cortices (Liu et al., 2009; Lyoo et al., 2006; Yuan et al., 2009) and increased white matter hyper-intensities, mainly in frontal areas (Lyoo et al., 2004).

Notably, these brain structure abnormalities are located in neural regions/networks associated with executive and attentional cognitive functions, such as the dorsolateral prefrontal cortex, anterior cingulate cortex and medio-temporal cortices. Chronic heroin-dependent individuals have been reported to show grey matter reductions in the left gyrus and cingulate gyrus within three days of abstinence (Wang et al., 2012). However, after one month of abstinence, there were no significant differences between patients and controls in any structural brain region (Wang et al., 2012). The mechanisms of this short-term change are unknown and studies on animals would be required to test whether abstinence was causal and reflected actual brain structure changes, or indirect changes (e.g. short-term changes in brain hydration due to a change in fluid intake during initial abstinence). Another study by Tolomeo et al., 2016 reported that MMT patients exhibited extensive grey matter reductions in the orbito-medial prefrontal cortex, bilateral caudate nucleus and globus pallidus (Tolomeo et al., 2016). Similarly, Tolomeo et

al., 2018 reported reduced white matter integrity in MMT individuals in comparison to healthy controls (Tolomeo et al., 2018). This is an empirical finding and the causal mechanisms are unknown, although direct and indirect effects of heroin use appear likely. In addition, as the study reported by Tolomeo and colleagues was cross-sectional, subjects at higher risk of developing opioid dependency may have reduced grey and white matter before exposure to opioids or abnormalities might reflect multiple episodes of hypoxia, e.g. occurring at night and during a respiratory infection, especially if additional illicit opioids and/or alcohol have been used to 'top-up' MMT. Longitudinal neuroimaging studies on patients and studies on animals would be required to test these hypotheses. In that context, it's important to note that most neuroimaging evidence is based on measures of brain structure or function in cross-sectional studies. We suggest that longitudinal studies are crucial to evaluate causality. Similarly, incentive salience deficits and deficits in reward processing (Koob and Volkow, 2016) might be driven by pre-existing vulnerability factors and by other environmental factors (e.g. peer pressure, stress and ready availability of drugs). Table 1 provides a summary of the long-term effects of heroin use on brain structure, cognition, psychiatric comorbidities and neurological disorders.

4.3. PET Studies

PET imaging studies by Volkow have reported a reduction in striatal dopamine D2 receptors (Volkow et al., 2002)which may be consistent with causal drug administration studies on animals (Volkow et al., 2002) and there are very

few studies of the opioid system in humans. D2 receptors play a crucial role in the motivational component of heroin addiction and chronic heroin use revealed changes in D2 receptor availability as shown by previous studies. Wang and colleagues reported that D2 receptor availability was lower than in controls (Gene Jack Wang et al., 1997). These findings were confirmed later by Zijlstra and colleagues who revealed lower baseline availability of D2 receptor in abstinent individuals (Zijlstra et al., 2008). In summary, this low availability of D2 receptors might play a role in the pathophysiology of addiction and relapse (Koob and Volkow, 2016).

4.4. Postmortem brain studies

Previous postmortem brain studies in chronic heroin users revealed elevated striatal levels of 5HT, whereas serotonin metabolite 5-hydroxyindoleacetic acid was significantly decreased compared to controls (Kish et al., 2001). Also, the same study found no difference in striatal dopamine (DA) transporter levels between chronic heroin users and controls (Kish et al., 2001). In addition, a post-mortem study of opioid-dependent individuals reported an increased prevalence of ischaemic brain lesions in the globus pallidus thought to be a specific effect of opioid-induced hypoxia (Andersen and Skullerud, 1999). Notably, lesions in the globus pallidus are a long-recognized consequence of heroin use and are thought to be related to hypoxic injury (Pearson et al., 1976).

5. Future directions: new hopes for treatment with clinical translation and implementation neuroscience

Available treatment options for opioid use disorder are limited in efficacy (Volkow, 2018) so the likelihood of returning long-term to normal life is limited. Whilst there is a clear consensus regarding neurobiological and neuropsychological abnormalities related to individuals with opioid use disorder, application of recent advances in neuroscience to clinical practice is rarely promoted (Verdejo-Garcia et al., 2019). We cover in the next section new directions that neuroscience-based interventions can bring to the treatment of opioid use disorder.

5.1. Pharmacological interventions

The FDA and other similar agencies globally have approved three medications for Heroin Use Disorder, namely Methadone, Naltrexone, and Buprenorphine; however, there is a clear need for new medications with higher treatment adherence, retention, lower abstinence rates and side effects (Kleber, 2007). Clinical trials using clinical outcome assessments (COAs) in drug addiction, such as urine drug tests, need large scale trials with long-term follow up and do not capture all relevant aspects of recovery or lack of it. Responding to this need, there is a new movement to apply neuroscience-based approaches that are reliable, sensitive to acute treatment response, and valid for addressing illness mechanisms involved in chronic heroin use disorder (Verdejo-Garcia et al., 2019). Targeting cognitive processes impaired in heroin using populations, such as self-control and

executive function with pharmacological interventions for cognitive enhancement, is another line of neuroscience research which may enhance the efficacy of existing medications (Verdejo-Garcia et al., 2019).

5.2. Cognitive interventions

With recent advances in the cognitive neuroscience and cognitive psychology of opioid use disorder, one can start to postulate how neuroscience can inform new generation of cognitive interventions to become an adjunct to current clinical practice. Few examples of the neuroscience-informed cognitive interventions and their preliminary evidence in substance use disorders in general and opioid use disorder in specific are summarized below into three main categories:

(a) Neuroscience-informed Psychoeducation and Metacognitive Training: Metacognition is thinking about one's thoughts. Poor metacognitive functioning relates to reduced consistency between subjective symptoms and real objective states (e.g. self-report craving and actual arousal states) (Castine et al., 2019) denial of problems associated with drug use (Moeller and Goldstein, 2014) and decreased interoceptive sensations (generated within the body) or awareness (Ateş Çöl et al., 2016). Accordingly, different interventions may enhance metacognition for opioid users. This includes 'motivational interviewing', which may enhance metacognition through improvements in insight and motivation for change (Apodaca and Longabaugh, 2009) as well as neuroscience-informed

psychoeducation programs aiming to improve a subject's awareness about their own mental health disorder and brain-related problems. Rezapour, et al., 2020, reported the feasibility and preliminary efficacy of a neuroscience informed psychoeducation intervention in a mixed group of opioid and meth users to improve metacognitive awareness (Rezapour et al., 2020) however, the evidence for long term efficacy of these interventions among opioid users is still missing.

(b) Neuroscience Informed Cognitive Modifications: The Cognitive Behavioural Therapy (CBT)-based model (Beck, 1979) for substance use disorders involves four main elements: triggers, thoughts/affect, craving and drug use (Larimer et al., 2003; Oei et al., 1991). In a cognitive neuroscience-informed approach, thoughts and craving can be delineated into 5 major cognitive processes, namely, attention, saliency valuation, memory, interoception and executive control. Each of these cognitive processes can be modified by cognitive interventions aimed at changing the cognitions elicited by drug/stress cue exposure to prevent relapse (Ekhtiari et al., 2017). As an example, attentional bias modification interventions have shown some promising results and some negative findings in modulating drug craving among substance users, however, there still a gap on rigorous studies in opioid use disorder (MacLean et al., 2018).

(c) Neurocognitive Rehabilitation: Neuropsychological (cognitive) impairments can interfere with treatment by reducing the ability of a user to receive, encode, integrate and employ therapeutic strategies, both in the context of treatment sessions and their everyday lives (Rezapour et al., 2016). There is a growing body of evidence for the effect of cognitive rehabilitation on attention, working

memory and executive functions to improve relapse rate among people with opioid use disorder (Rezapour et al., 2019).

5.3. Technology-based Neuromodulation Interventions

Different neuromodulatory interventions including non-invasive brain stimulation technologies and neurofeedback have shown preliminary but promising results in treatment of opioid use disorder. Neurofeedback is a technique that helps patients to modulate their brain activity into a target state. Real-time brain activity is represented as visual or auditory feedback (e.g. a car driving on the road with speed related to the brain activity) and patients learn to change their brain activity from an undesired state to a desired state and monitor the results through feedback (e.g. changing the speed of the car). These practices can include not thinking about drug-related memories and/or remembering happy memories instead. Two types of neurofeedback have been used to in opioid use disorder; EEG and fMRI neurofeedback, which differ in the type brain measurements; i.e., the activity of a brain region/network of interest with fMRI and recorded electrical activity from a set of electrodes in EEG. Psychological and behavioural improvements have been reported in substance use disorders (SUDs) treated by EEG or fMRI neurofeedback: amongst 15 studies (7 for EEG and 8 for fMRI) that investigated the effects of neurofeedback (EEG or fMRI) on SUDs reported up until July 2019, two studies used EEG-neurofeedback, reporting that this technique had positive outcomes on opioid use disorder (Luigjes et al., 2019; Verdejo-Garcia et al., 2019). The first study published in 2010, used 30 sessions of neurofeedback with 20 opioid-

dependant patients and reported a significant reduction in heroin craving (Arani et al., 2010). In the following study by the same group, the same protocol with different targets resulted in improvement in somatic symptoms of drug use, mood, and a total score reflecting general mental health, with a reduction in anticipation of positive outcome and desire to use opioids, and some relief from withdrawal of craving (Dehghani-Arani et al., 2013). These studies are preliminary and much more work would be required to develop an effective widely available service for people with opioid use disorder.

Over 80 clinical trials with transcranial Electrical Stimulation (tES) and Transcranial Magnetic Stimulation (TMS) have been reported although very few of them on opioid use disorder (Verdejo-Garcia et al., 2019). This suggests a possibility for using such techniques as an adjuvant to conventional addiction treatments, to reduce drug craving, improving cognitive control, and mitigating withdrawal negative affect (Ekhtiari et al., 2019). A recently published tES study (reported that anodal transcranial direct current stimulation (tDCS) to the right dorsolateral prefrontal cortex significantly reduced drug craving, depression, and anxiety symptoms amongst people with opioid use disorder (Taremian et al., 2019). In another study by Wang et al., 2016, bilateral tDCS over frontal and temporoparietal regions reduced craving scores in heroin users (Wang et al., 2016). In another trial, Shen et al. reported that a single session of 10 Hz repetitive TMS over the left dorsolateral prefrontal cortex reduced cue-induced craving in heroin users (Shen et al., 2016). A few years later, the same group reported that use of a similar TMS protocol in multiple sessions improved sleep quality and low mood/increased anxiety among a mixed group of opioid and methamphetamine

users (Lin et al., 2019). However, these studies are still preliminary and clear demonstration of the presence or absence of any clinically meaningful effects on opioid use disorder requires further investigations.

6. Conclusion

Despite the growing global burden of opioid use disorder, knowledge of the long-term brain effects of heroin use disorder is limited. Although there is a consensus that altered brain structure and function may underpin opioid use disorder, clinicians working in addiction treatments centres rarely incorporate neuroscience-informed approaches into their practice.Two assessment areas have been highlighted: cognitive assessment and neuroimaging, and two interventional areas: cognitive training/remediation and neuromodulation. Integration of neuroscience- based approaches can be best achieved by promoting international collaboration between researchers and clinicians, developing harmonised protocols and data management systems, and prioritising multi-site research that focuses on improving clinical outcomes (Verdejo-Garcia et al., 2019). Future longitudinal studies are required to unravel the mechanisms of action and role of co-existing psychiatric disorders and cognitive impairments.

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